

ON THE
PATHOLOGY OF PAGET'S DISEASE OF THE NIPPLE.

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IN the July number, 1883, of this Journal, one of us (Dr. Duhring) reported two cases of Paget's disease of the nipple, referring only to the clinical features of the disease. The notes below recorded deal with the specimen of the first of these cases.

The relation between certain diseased processes of the nipple and areola, and the subsequent development of mammary cancer, first pointed out by Paget, has already evoked some discussion. The importance of the subject is apparent, and it ultimately resolves itself into the question of distinguishing between ordinary eczema of the nipple and another similar cutaneous pathological process which on good grounds is believed to lead to the formation of malignant disease of the mammary gland.

The histology of the two diseases, as already indicated by Thin (*Brit. Med. Jour.*, May, 1881) in an able article on this subject, is distinct. He says, "The microscopical examination is decisive on this point, and proves definitely that the disease is not eczema." But the question of paramount interest and importance is to settle the exact relation between the cutaneous affection and the subsequent development of cancer in the gland. There is supposed, by the best authorities, to exist a causative relation between the first and second.

Paget (*St. Barthol. Hosp. Reports*, 1874, p. 83) was the first to call attention to this affection, and pointed out the relation between surface irritation and the development of cancer, *e. g.*, epithelioma of the lip.

Busch (*Langenbeck's Archiv*, Bd. xxi. p. 673) maintains that the beginning of destructive epithelial cancer is, in many cases, simple epithelial proliferation on the outer surface of the skin; that the collection of epithelial masses about the nipple may cause retention of secretion, and under circumstances lead to cancer.

The manner in which chronic cutaneous inflammation of the nipple leads to the development of cancer is still a subject of dispute. Butlin (*Med. Chirurg. Trans.*, vol. lx. p. 153) concludes that after a time the epithelial lining of the lactiferous ducts became affected, and that the disease travelled along the larger ducts reaching the smaller ducts and finally the acini which became dilated, filled with proliferating epithelium that, at length, escaped into the surrounding tissue. Thin (*Brit. Med. Jour.*, May, 1881) believes that the cancerous formation is the result of an abnormal development of duct epithelium, and that the skin affection is secondary "to a destroying agent extending from the mouths of the lactiferous ducts into the surrounding papillary layer." "The development of malignant papillary dermatitis of the nipple is suggestive of the escape of a fluid through the mouths of the ducts, which possesses the corrosive qualities of cancerous epithelium." He regards the new formation as a duct cancer, and believes that "cancerous changes are developing in the ducts long before they give rise to sufficient indurations to produce a palpable tumour."

As to the microscopic appearance of the tissues of most of the cases thus far presented, there is a striking similarity. Butlin (*Med. Chirurg. Trans.*, vol. lix. p. 108) presented two cases, and in one of them the mucous layer of the epidermis had undergone proliferation and thickening, and the corium and subcutaneous connective tissue were indurated and infiltrated by small round cells. The lactiferous ducts were found widely open and distended, not lined by cylindrical epithelium, but containing large masses of epithelium of a squamous and glandular type. Some of the ducts were seen completely filled, so as to present the appearance of sections of tubes in tubal nephritis. The immediate vicinity of the ducts was also the seat of a small round cell infiltration, which Butlin claimed has some relation to the proliferation of the duct epithelium. Waldeyer (*Virch. Archiv*, Bd. lv. p. 124) also speaks of the intra-acinous granulation growth in connection with the development of the epithelium in the formation of cancer. Butlin (*Med. Chirurg. Trans.*, vol. lx. p. 153) presented two other cases of cancer of breast, preceded by eczema of the nipple and areola, in which there were observed in the cutaneous tissues changes similar to those of the two previous cases, and in addition, a dipping down of the epidermis into the cutis, and the presence of a few cell nests, giving the thickened portions the appearance of an epithelioma. In the tissue of the gland the partition walls of the acini and ducts were

broken down and the epithelial contents had made their way into the surrounding tissue.

In his conclusions Butlin claimed that one of the effects of the eczema was to produce a proliferation of the mucous layer of the epidermis; that in time the epithelial lining of the lactiferous ducts became affected; that the disease travelled along the larger ducts, reaching the smaller ducts and the acini, which became dilated and filled with proliferating epithelium, that at length discharged into the surrounding tissues; finally, that cancer thus formed was essentially a disease of the epithelium.

Lawson (*Clin. Soc. Trans.*, vol. xiv. p. 222) presented a case of eczema of the nipple, in which the breast was removed and examined microscopically by Dr. Thin. The latter found it almost entirely composed of fat permeated by streaks of connective tissue, which, under the microscope, was found to consist of white fibrous tissue, in which were lodged epithelial tubes of various sizes, having a small columnar epithelium lining. A similar condition was found in our case, to be referred to presently. Thin called it adeno-lipoma. The skin was the seat of malignant papillary dermatitis, many of the cells of the rete being degenerated, while the corium contained a stratum of dense cell infiltration.

Morris (*Med. Chirurg. Trans.*, lxiii. p. 87) described two cases, in the first of which the mammary gland was in a condition of atrophy, represented by straggling fibrous bands in a substance of fat; the skin was crowded with a cell-infiltration, while the lactiferous tubes were filled with epithelium. In the second case the examination was made by Thin, and showed cancer of the gland. Sections through the nipple showed tubes filled with epithelium, and sections of skin revealed the almost total absence of the epidermis, a ragged remnant of the rete, and the epithelium in a process of degeneration. The papillary layer of the corium was congested and filled with exudation cells, while the pars reticularis was mostly normal.

Porter (*Boston Med. and Surg. Journal*, May, 1872) reported a case of chronic destructive inflammation, in which the papillæ of the corium abruptly changed their character, becoming much elongated, covered and surrounded by an increased quantity of epithelium. The subcutaneous tissue was observed to be thickened and infiltrated with small cells, and while some of the milk ducts of the nipple were of normal size and lined with a single layer of epithelium, others were packed with epithelium, and the neighbourhood was seen to contain numerous cancer nests. The tissue of the mammary gland showed commencing cancerous degeneration; the nipple was entirely destroyed.

De Schweinitz (*Medical News*, February 9, 1884) describes a case of Paget's disease, followed by cancer of the mammary gland, in which there were proliferation and degeneration of the mucous layer of the epidermis, also an extension downward. The papillary layer was found to be the

seat of a dense, small, round-cell infiltration, at times hiding all trace of normal structure ; the lymph spaces in the subcutaneous tissue were seen to contain varying amounts of epithelium ; the lactiferous ducts were found choked up with proliferating epithelium, which was seen escaping into the surrounding connective tissue, there forming alveoli of true scirrhus cancer. The gland tissue contained alveoli of spheroidal epithelial cells similar to those found in the subcutaneous connective tissue.

Dr. De Schweinitz has kindly furnished us with specimens of tissue from his case, from which sections were made for comparison with those obtained from our own case. These sections, examined under low magnifying power (50 diameters), show here and there a slight, thin remnant of the horny layer of the epidermis, and a marked thickening of the upper layers of the rete, where it is present, while the papillary layer of the rete is seen to send insinuating prolongations into the tissues of the cutis. The papillary layer of the corium is for the most part substituted by the proliferating rete and a dense cellular infiltration, and the papillæ, where present, lie exposed and fringed with a few adherent rete cells. The upper and middle layers of the corium contain slight perivascular inflammatory exudations, while the lower layers and subcutaneous connective tissue are the seat of variously-sized alveoli of scirrhus cancer, as has been clearly described by Dr. De Schweinitz.

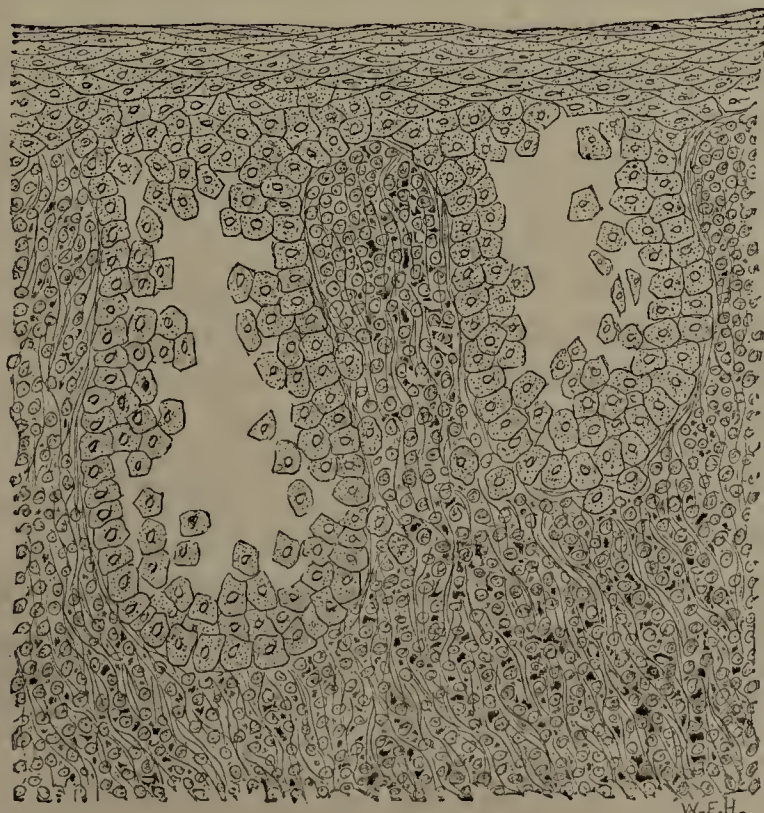
Under higher power (250 diameters) the rete is seen to be in an active state of proliferation, the cells forming in a peculiar concentric manner, to be fully described presently, burrowing downwards into the corium and extending laterally, thus compressing the papillæ, making the latter appear in many places as a mere narrow column of cells. The layers of the corium immediately beneath the papillæ contain an often dense infiltration of small round cells which, where the papillæ are present, extend into them, hiding all trace of their normal structure. The subcutaneous connective tissue bordering on the site of the nipple contains small alveoli of epithelial cells, which increase in number and size as the lactiferous ducts are approached. On account of the stratified condition of this cutaneous tissue, these alveoli may be seen to assume, at first, a linear form, later becoming ovoid. The larger lactiferous ducts are everywhere seen filled with an exuberant growth of epithelium, which in many places has penetrated the walls of the ducts and escaped into the surrounding tissue. Two of these larger ducts, however, while crowded with epithelial cells are seen to have intact walls, and the surrounding tissue is free from cancerous growth.

The notes about to be presented were derived from a study of our own case. Examination of sections through the nipple, perpendicular to the surface, under a magnifying power of fifty diameters reveals the following :—

The surface of the lesion is almost denuded of the horny layer of the epidermis, here and there small islets of the same being seen which form thin, dry, loosely adherent, and partially exfoliated layers. Just over the centre of the nipple the rete Malpighii presents an irregular broken surface, in some places being entirely absent so as to expose the papillæ of the corium. The rete is in a condition of disorganization, and seems loosely attached to the corium. Proceeding towards the periphery, this disorganization grows less and less, and in its place is a condition of increased cell growth. Many variously sized empty spaces may be noticed in the papillary layer of the rete, also between it and the corium. The papillæ of the corium are for the most part crowded with a cellular infiltration to such an extent as to change the form, size, and general appearances, even to hide all traces of their normal structure. Some are enlarged to twice their normal size, and constricted to various degrees at their bases; others are compressed laterally, and present the appearance of a narrow column of cells. Occasionally they are entirely obliterated, their places being marked by small heaps of cellular material. Proceeding peripherally, the cellular infiltration of the corium becomes so dense as to almost obliterate the boundaries between it and the epidermis. Passing into the lower layers of the corium strands running perpendicularly and obliquely downwards, and variously sized and shaped clusters and aggregations of small round cells may be seen.

Under a magnifying power of 250 diameters a more intimate knowledge of the tissue components and various structural changes are made apparent. The epithelial cells of the horny layer had absorbed the staining fluid to a slight extent, and their nuclei are well marked. The cells of the rete are seen in various stages between active proliferation and degeneration. In each interpapillary projection of the rete there is formed an alveolus with a central zone of degeneration and a peripheral zone of proliferation and growth (Fig. 1). In some places indications of the formation of alveoli

Fig. 1.



may be seen in that the cells are beginning to assume a concentric arrangement. In other places the disorganization of the epidermis is complete, and nothing remains but a nest of cells. As this cell growth advances the papillæ of the corium are encroached upon, become œdematous, compressed, and constricted at their bases (Fig. 2).

Fig. 2.



The cells composing the peripheral zone of the alveoli are of the epithelial type, of squamous and cuboidal variety, have an abundance of protoplasm, and one or several nuclei which are irregular in shape and have a granular contents. Close observation shows the cells to exist in various forms, some being round, some oval, some elongated and spindle shaped, exhibiting a disposition to divide in the centre to form two cells. The cells of the central zone are more or less granular, and exhibit evidences of fatty degeneration. This condition of proliferation agrees with an observation made by Butlin (*Med.-Chirurg. Trans.*, vol. lix. p. 108, also vol. lx. p. 153), that "the mucous layer had undergone proliferation, and was thickened, and here and there dipping down into the cutis." The same appearances and arrangement of cells in the rete may also be noticed in the specimens from the case of Dr. De Schweinitz. There is no doubt in our minds as to the relation of the alteration and obliteration of the papillæ of the corium to the proliferation of the rete. As the epithelial cell growth of the rete advances downwards, the bases of the papillæ become more and more constricted, causing the papillæ first to assume a pyriform shape, as in Fig. 2; then the pressure being continued on the papillary capillaries causes the upper ends of the papillæ to swell and become filled with a lymphoid cell exudation. The papillæ finally become detached, and one sees alveoli of lymphoid cells in the midst of a dense epithelial cell mass. These lymphoid cell alveoli undergo degeneration, drop out and give rise to some of the numerous empty spaces found in the rete.¹

¹ It may occur to some, that these appearances were all due to the fact that the sections were cut obliquely, but this was not the case, as great care was taken to make the sections as nearly perpendicular to the surface as possible.

The strands and aggregations of small, round cells, scattered about in the layers of the corium are perivascular lymphoid exudations of an inflammatory type. In many places arterioles and capillaries may be seen in transverse and longitudinal section, surrounded to a greater or less extent with such collections of cells.

In the middle and lower layers of the corium are found alveoli of various sizes and shapes, completely or partially filled with epithelial cells, which are regarded as true and typical carcinomatous formations. The alveoli are surrounded by a dense stroma of connective tissue, in the meshes of which may be found a varying amount of lymphoid cellular material. The connective tissue forming the stroma is in some places embryonic in character, especially where the perivascular exudation referred to above exists in large amounts; in other places it may be seen to form large, thick bundles penetrated in every direction by the insinuating, destructive, solid pegs of epithelium. On the other hand, it is seen in thin atrophic bundles, resembling greatly cicatricial tissue. This is particularly the case just under the site of the nipple, and extending downwards. Sections made from the tissue about one and one-half inches below the surface reveal only bands of dense, atrophic, connective tissue surrounded by adipose tissue, without a vestige of gland structure or lactiferous tubules, just as also described in the cases of Lawson and Morris above referred to. This condition would lead us to regard the new formation as an *atrophying scirrhus*. Nowhere is there to be seen any evidence of the formation of cysts, as was the case in Thin's specimen. There is, in other words, no resemblance to the "fibro-carcinoma cysticum mammae" of Waldeyer. The dense atrophic, cicatricial-like connective tissue immediately under the site of the nipple and extending downward may have contributed much in bringing about the retraction of the nipple which is so characteristic of Paget's disease.

The large lactiferous ducts about one-quarter of an inch below the surface are seen with their lumina partially or completely filled with epithelial cells. The elastic layer of Henle and the inner layers composing the duct walls are intact, and nowhere give evidence of perforation on the part of the contained epithelium. The same is found to be the condition of two large lactiferous ducts in the specimen from the case of Dr. De Schweinitz. The tissue in the immediate neighbourhood of these ducts is made up of loose connective tissue which is the seat of a dense small-cell infiltration. The smaller lactiferous tubules found about three-quarters of an inch below the surface are also seen to contain varying amounts of epithelium, but the duct walls are not everywhere found to be intact. Cells may be seen between the layers composing the walls, and in some places in considerable amounts, while occasionally a breach through the entire wall is observed and in the vicinity are large cancer alveoli. Thin has also pointed out certain "finger-like columns which had broken through the wall of the duct and advanced into the elastic layer," which condition is applied to the larger ducts, and not as in our case to the smaller ones.

One of the striking features of the specimen, a feature which was also called attention to by Thin, is the comparative little change in the layers of the corium immediately beneath the papillæ, notwithstanding the profound changes above and below. In fact the only pathological deviation here consists in the perivascular exudations. This fact, it seems to us, has some bearing upon the direction in which the new growth is advancing, careful examination and comparison of sections showing that the epithelial

pegs or radicles are creeping upwards and outwards. The alveoli are largest in the lower part of the specimen, and gradually diminish in size as the surface or lateral part is approached, while the upper layers of the corium are not yet involved, all of which indicates that the centre of growth is in the region of the smaller collecting ducts, about one inch or three-quarters inch below the surface. This is supported by the fact that the walls of the larger ducts are intact and their immediate vicinity is entirely free from cancerous infiltration.

Sections taken from the border of the cutaneous tissue present an histological picture which confirms the clinical fact that the disease is sharply defined and ends abruptly. The transition from healthy to diseased tissue is characterized by a sudden descent caused by the lymphoid infiltration of the papillary layer of the corium, and the beginning alterations in the rete Malpighii. The appearance corresponds with that described by Thin as follows: "The line of demarcation is indicated sharply by the projection downwards into the cutis of a rounded wall of epidermis, on the further or healthy side of which the cell exudation ceases."

Finally, the question arises as to the relation between the affection of the skin and the cancer new formation. The view adopted is one based on one side upon the minute anatomy of the part, and on the other upon the histological facts presented by the specimens. The disease is regarded as an abnormal epithelial cell proliferation which begins in the rete Malpighii. Anatomically the lining membrane of the lactiferous ducts is a continuation or simple indentation of the epithelial layers of the epidermis, and by continuity the tendency or impetus to growth which characterizes the epithelium of the rete in this disease, is communicated to the cells of the ducts, and as the growth proceeds the lumina of the ducts soon become filled with cells. Advancing from the surface towards the interior the ducts grow smaller by ramification, and their walls grow correspondingly thinner. The larger tubes, of which there are twelve to twenty, are surrounded, in addition to the fibrous and muscular coats, by a tough, elastic layer described by Henle. This is barely present in the smaller tubes, and as a consequence the walls of the smaller tubes first give way, and the epithelium makes its way into the surrounding tissue and advances towards the surface as described. This observation is also confirmed by the condition of the ducts found by us in Dr. De Schweinitz's case, though to a less extent because the specimens represented a more advanced stage of the disease.

Summary.—1. Horny layer of epidermis present in thin, loosely adherent, partially exfoliated layers, and in some places absent, so as to expose the papillæ of the rete Malpighii, which in turn is occasionally absent, exposing the papillæ of the corium.

2. The rete Malpighii is in a condition of abnormal growth and degeneration. In each papilla there is formed an alveolus, or concentric arrangement of the cells, in which there is a central zone of degeneration and a peripheral zone of proliferation.

3. The papillæ of the corium, infiltrated by dense masses of lymphoid cells, are encroached upon, compressed, and finally obliterated by the proliferating rete.

4. The upper layers of the corium, with the exception of a varying amount of perivascular lymphoid exudation, are the seat of little change.

5. In the middle and lower layers are variously sized alveoli of epithelial cells, regarded as typical cancer new-formation.

6. The stroma, in more recent formations, is embryonic; in later stages it is atrophic, almost cicatricial.

7. The cicatricial-like connective-tissue, under the site of the nipple, may contribute much in bringing about retraction.

8. The larger lactiferous ducts, though carcinomatous change has already taken place in them, are present with intact walls. They are filled with epithelial cells. The smaller ducts are also filled with cells, and occasionally a breach through the entire wall is observed, and, in the immediate vicinity, typical cancer structure may be seen.

9. Sections from the border of the diseased cutaneous tissue show a sudden transition from healthy to diseased structure.

10. The affection is regarded as an abnormal proliferation and degeneration of the rete, with secondary destruction of the papillæ of the corium, and subsequent development of scirrhus cancer of the atrophying variety.

11. The cancerous change takes its origin from the epithelium of the smaller ducts, and advances from below upwards and outwards as far as the skin is concerned; later it attacks the gland structure.

12. The retraction of the nipple is an early sign of carcinomatous change.

